REMARKS

Claims 19-39 were previously pending in this application. Claims 19-39 are still pending for examination with claim 19 being an independent claim. No claims have been amended, canceled or added. No new matter has been added.

Objection to Information Disclosure Statement (IDS)

The Examiner has requested a list of co-pending applications as well as a copy of the references cited in co-pending Application No. 08/738,652, now with the Board of Interferences. A list of co-pending applications and the references cited in Application No. 08/738,652 were submitted on January 23, 2007. Applicants respectfully request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants.

Double Patenting Rejection

Claims 19-39 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-49 of U.S. Patent No. 6,239,116.

Claims 19-39 were not obvious at the time of the invention over claims 1-19 of U.S. Patent No. 6,239,116 because claims 1-19 of U.S. Patent No. 6,239,116 do not suggest that the CpG oligonucleotide be administered to a subject having asthma. Claims 1-19 of the '116 Patent are directed to a method for inducing IL-6 in a subject. The *claims* of the '116 Patent do not include any reference to allergens or asthma. The currently pending claims, by contrast, include the limitation that the CpG oligonucleotide is administered to a subject to treat asthma. In the most recent Office Action, the Examiner objected to this distinction, stating that the patent specification of the '116 Patent teaches that nucleic acids can be administered to a subject to shift an immune response from Th2 to Th1 and to treat asthma. Applicants respectfully disagree that the appropriate legal standard is being applied.

A prima facie case for obviousness type double patenting has not been established. According to MPEP 804 "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent,

the disclosure of the patent may not be used as prior art." The Examiner has based the rejection of claims 19-39 on the teachings found in the specification of the '116 patent, rather than the claims. The claims of the '116 patent do not recite a method of shifting an immune response to TH1 or methods of treating asthma. It would be clear to one of ordinary skill in the art that Claim 19 (and its dependent claims) relates to a subject that has asthma and that the claims of the '116 Patent do not. Accordingly, Applicants respectfully request the Examiner reconsider the double patenting rejection with respect to claims 1-19 of the '116 Patent.

Claims 19-39 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 of copending Application No. 09/337584.

The rejection is a provisional one since none of the claims in the 09/337584 application have been found allowable. If any of the cited claims are found allowable, Applicants will address the rejection.

Claims 19-39 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46, 52, 64, 71, 72, 74, and 80 of copending Application No. 10/613,739.

The rejection is a provisional one since none of the claims in the 10/613739 application has been found allowable. If any of the cited claims are found allowable, Applicants will address the rejection.

Claims 19-39 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 and 31-33 of copending Application No. 10/894,862.

The rejection is a provisional one since none of the claims in the 10/894,862 application has been found allowable. If any of the cited claims are found allowable, Applicants will address the rejection.

Claims 19-39 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42, 45-53, 57-60 of copending Application No. 09/337,893.

The rejection is a provisional one since none of the claims in the 09/337,893 application has been found allowable. If any of the cited claims are found allowable, Applicants will address the rejection.

Rejections Under 35 U.S.C. 112

Claims 19-39 have been rejected under 35 U.S.C. 112, first paragraph, because according to the Examiner "the specification, while being enabling for a method for treating asthma is a subject (murine model), comprising administering to a subject an immunostimulatory oligonucleotide (CpG, specifically SEQ ID NO: 10), does not reasonably provide enablement for a method for treating asthma in a subject (animal or human), comprising administering to a subject (animal or human) an immunostimulatory oligonucleotide (CpG, the scope of the myriad possible immunostimulatory oligonucleotides encompassed by the claims)."

The Examiner has maintained the rejection of the claims of record under 35 U.S.C. §112. Pages 7-21 of the Office Action dated December 5, 2006 repeat the rejection found in the Office Action dated April 24, 2006. The first full paragraph on Page 21 of the Office Action addresses the Examiner's reasons for maintaining the rejection for lack of enablement. Each of these issues is addressed herein. The reasons for maintaining the rejection are addressed first.

Response to the Examiner's reasons for maintaining the rejection:

The Examiner has stated that the rejection is maintained for the reasons of record that have been previously addressed. Applicants disagree. Applicants have presented many arguments establishing that the claims are enabled and that the rejection should not be maintained. The Examiner has not addressed these arguments. Applicants reiterate these arguments below and requests a response if the rejection is to be maintained.

Additionally the Examiner has noted that Applicants have argued previously in regard to Kim et al. that the "claims are not directed to safety and that safety is not a consideration when determining enablement of the claimed invention." Applicants disagree. Applicants never argued that the "claims are not directed to safety" or that "safety is not a consideration". To avoid any

confusion the entirety of applicants arguments with respect to Kim et al that were provided in the Reply to Office Action dated August 24, 2006 are presented below.

"In response to the July 6, 2005 Office Action, Applicants pointed out that several Phase I and Phase II human studies using subcutaneously administered CpG oligonucleotides have been performed to date in cancer trials, and that those studies demonstrate that CpG oligonucleotides, even in aggressive doses, are well tolerated by humans. The Examiner responded that the trials in question were for cancer, while the pending claims are directed to treatments for asthma and allergy, not cancer. Applicants submit that the evidence of human tolerance in the Kim et al 2004 abstract are, in fact, relevant to the safety of the methods encompassed by the pending claims regardless of the ultimate purpose of the CpG oligonucleotide treatment. Kim et al 2004 shows that CpG oligonucleotides are well tolerated by humans. That result does not depend on the therapeutic purpose of the CpG treatment. If CpG oligonucleotides are well tolerated when administered to a cancer patient, there is no reason to expect adverse effects when the oligonucleotides are administered to an asthmatic patient. Accordingly, Kim et al is relevant evidence of the safety of the claimed methods."

Applicants have presented the teachings of Kim et al to rebut a rejection that administration of oligonucleotides was unsafe. Applicants did not say that safety is not a consideration when determining enablement of the claimed invention. It is respectfully requested that Applicants arguments be considered and the rejection be withdrawn or if they are maintained that sound reasoning be provided to support the maintenance of the rejection.

Rejections repeated from prior office action but not addressed:

As discussed above, the Examiner re-iterated most of the rejections under 35 USC 112 presented in the prior Office Action dated April 24, 2006. Other than the specific points discussed above, the Examiner has not addressed any of Applicants' arguments filed in response to the Office Action dated April 24, 2006. Thus, Applicants present arguments to address each of these rejections again. It is specifically requested that the Examiner address each of Applicants' arguments or withdraw the rejections.

The Examiner stated that examples of induction of interleukins in spleen, liver, or thymus cells are not representative of successful treatment of asthma using any CpG containing oligonucleotide because the specification does not teach a correlation between in vitro IL-6 induction and *in vivo* asthma treatment. (Office Action Pages 14-15 and 17-18.) Applicants respectfully disagree.

Initially, Applicants point out that a significant amount of data is provided in the specification. The data is not limited to the IL6 data. It is the data in the aggregate that support the claimed invention. The data correlate with the scope of the claimed invention. Applicants have included many examples in the specification including induction of cytokines such as IL-6, IL-12 and IFN-gamma. The data in the application, includes that represented in Tables 1-3, which establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Th1 response. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides. The combination of these changes in immune parameters was adequate to demonstrate to one of skill in the art at the time of the filing of the priority patent application that CpG oligonucleotides would be useful in the treatment of asthma. Applicants assert that a correlation between CpG and their use in the treatment of asthma is disclosed and enabled.

Additionally, the specification does teach that redirecting immune response from Th2 to Th1 is useful in the treatment or prevention of asthma. For example, on Page 8 Lines 11-13, the specification states that "by redirecting a subject's immune response from Th2 to Th1, the instant claimed nucleic acid modules can be administered to treat or prevent the symptoms of asthma." The specification also teaches that Th1 cytokines can suppress the formation of Th2 clones, and that Th2 clones are known to be elevated in asthmatic subjects. See Page 41 Lines 33-38. Accordingly, the specification does teach a correlation between the specific cytokine induction and *in vivo* asthma treatment.

The examiner has cited McCluskie et al 1999 (Molecular Med. 1999, 5/5:287-300) for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. (Office Action Pages 9 and 19-20.)

Applicants responded that McCluskie is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The examiner responded that the claims "do not specifically exclude plasmids, vectors, or DNA vaccines. The immunostimulatory nucleic acid could read on the whole bacteria, or [...] could be part of a DNA vaccine." (Office Action Pages 19-20.) The pending claims do not relate to DNA encoding a particular antigen to which an immune response is desired. The pending claims describe the use of an oligonucleotide, which is not a plasmid.

McCluskie discusses the variable therapeutic effectiveness of DNA vaccines wherein a plasmid is introduced into non-human primates and mice. The plasmid DNA in McCluskie encodes a particular antigen, namely either the middle or major surface protein of the hepatitis B virus. (See Page 289.) The immunity mechanism discussed in McCluskie relates to the expression of that antigen to generate an immune response. Additionally, the key feature of the pending claims is the CpG motif, not a DNA sequence encoding a particular protein antigen. The variable therapeutic response discussed in McCluskie concerns the immune response to the antigen (surface proteins from the hepatitis B virus) and is thus not relevant to the enablement of the pending claims which concern shifting immune response from Th2 to Th1 to treat asthma. McCluskie does not show unpredictability of the latter effect (shift from Th2 to Th1), only the former (immune response to plasmid DNA encoding antigen). Applicants respectfully request that the Examiner reconsider the enablement rejection in light of this distinction.

The Examiner has cited Krieg et al 2000, Wohlleben et al 2001, Kline et al 2002, Kline et al 1998, Weiner et al 2000, Agrawal et al 2000, Satoh et al 2002, Dziadzio et al 2004, Barnes 2000, and Van Uden et al 1999 for the proposition that the state of the art is unpredictable with respect to the effectiveness of the claimed method. In response, Applicants provided a detailed explanation for each reference as to why the reference actually shows that the claimed method is promising as a treatment for asthma and that none of the references show that CpG oligonucleotides would be unsuitable for treatment of asthma. The Examiner responded that "even though these references may suggest the possibility if CpG's usefulness in treating a subject having asthma, they still also indicate even several years after Applicants' effective filing date that the scope of the claimed method is not enabled." (page 20.) Applicants respectfully submit that the Examiner has not met

the burden of showing lack of enablement. The Examiner did not respond to Applicants' explanations as to why none of the references showed that CpG oligonucleotides would be unsuitable or unpredictable as an asthma treatment, instead the Examiner only stated that the references indicated the claims were not enabled. Applicants request the Examiner reconsider Applicants' explanations in response to the July 6, 2005 Office Action which show that none of the above-cited references indicate any lack of enablement. For purposes of completeness, Applicants have re-presented those arguments in their entirety below.

Krieg et al 2000 (Immunology Today 2000, 21/10:521-526) has been cited for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. Krieg et al is a review article describing the uses of CpG oligonucleotides. The office action specifically points to page 524 of the reference in support of the examiner's argument that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. Applicants do not see this teaching in the reference. In fact the reference teaches on page 524 that "Unlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." This teaching does not support the examiner's assertion that the administration of CpG oligonucleotides varies depending on the organism. Furthermore, Krieg et al describe the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 of Krieg et al includes the following teaching:

> "These and subsequent studies have shown CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of immunization including mucosal immunization (reviewed in Ref. 50). In fact, in a comparison of 19 different adjuvants, CpG DNA was found to be the strongest for inducing Th1-like immune response to tumor antigens[51]" and
> "The potent Th1 adjuvant effect of CpG can even override preexisting Th2 immune responses [5, 47]; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation ..... It should be stressed that CpG DNA is effective in asthma

immunotherapy even when given as a stand-alone agent without allergen." [Emphasis added]

The Examiner has cited Wohleben et al (TRENDS in Immunology, 2001 22/11:618-626) in support of 2 arguments: 1) that the "state of the art questions whether 'CpG-ODNs can be used in humans to inhibit the development of asthma?'" and 2) that Wohleben teaches that "all approaches that induce Th1 responses have the potential side-effects of Th1cell-mediated inflammation potentially causing serious tissue damage." The applicants respectfully disagree with the Examiner's characterization of the reference.

Wohleben et al actually provides a favorable view of CpG oligonucleotides and their usefulness in the treatment of asthma. The use of CpG oligonucleotides is identified in the abstract and conclusion of the paper as one of "the most promising approaches" for the treatment of atopic disease and particularly asthma. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans. It is taught that the "results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders." (Page 620 second column first paragraph, emphasis added) and "This suggests that the treatment of humans with CpG-ODNs could be very effective in inhibiting the development of asthma." (Page 620 second column first paragraph). Thus, the teachings found in Wohleben et al are not sufficient evidence that the invention was not enabled at the time of filing of the patent application.

Further, the teachings of Wohleben et al with respect to potential side effects do not support a lack of enablement of the claims. Wohleben et al teach on page 620 immediately following the discussion of side effects that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." (Page 620 second column first paragraph). Additionally the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. MPEP2164.01(c). "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement.

Furthermore, the Wohleben et al reference, as well as the others cited for safety concerns and discussed in more detail below, do not suggest that use of CpG would be unsafe. All drugs

have some side effects. The references at best suggest that care should be taken to see if there may be certain patients for which the compound might be contraindicated. This is the type of inquiry made by those of ordinary skill in the art respecting all drugs. There is no evidence in any of the cited papers that CpG oligonucleotides would be unsuitable for the treatment of asthma. To the contrary, the cited papers, published years after the filing date, continue to support the view that CpG oligonucleotides should be advanced through clinical trials for the treatment of asthma. One of ordinary skill in the art would have believed, based on the data in the application, that CpG oligonucleotides would be well suited as clinical trial candidates for the treatment of asthma. The papers cited for safety issues have not altered that view.

The Examiner has cited the Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179) and Kline et al 1998 (J Immunol 1998, 160: 2555-2559) references to demonstrate that the use of CpG alone in some instances is not effective for the treatment of asthma. The Examiner asserts that Kline 2002 teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model. The section of the paper identified by the Examiner on page L172 relates to an experiment designed to model "persistent asthma in humans, who, by current standards of treatment, require intensive anti-inflammatory therapy." The claimed invention does not require that persistent asthma be treated with a single dose of CpG. Doses are within the purview of those skilled in the art, and the data in the paper supports that monotherapy at appropriate doses can work. In fact, many drugs including other drugs for treating chronic asthma are not effective as a single dose.

The Examiner has also indicated that Kline 2002 teaches that "splenocytes from OVA-treated mice did not develop an antigen specific Th1 phenotype. However mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2)." This statement does not support a lack of enablement of the claimed invention. The lack of development of a Th1 phenotype in mice in response to OVA treatment is not inconsistent with the invention.

Weiner (J. Leukocyte Biology, 2000, 68:456-463) is cited for the proposition that the molecular mechanism of CpG is unknown. Knowledge of the mechanism of action isn't necessary, particularly in view of the detailed knowledge at the time the patent application was filed of the

cellular effects of CpG oligonucleotides. The patent application identifies consistent changes in the immune system at the cellular level that occur in response to CpG administration and which are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance it is taught on page 456 1st column second full paragraph that "Studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." Page 457 under "In vivo effects of CpG ODN" teaches that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al (Molecular Med. Today 2000, 6:72-81) has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make one of 3 modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification teaches that a CpG containing oligonucleotide has an unmethylated C in the CpG motif. Further, the cited section of Agrawal et al teaches that the proposed 3 modifications "significantly reduced side effects". Agrawal et al does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

Satoh et al. (Fukushima Igaku Zasshi 2002, 52/3:237-250) was cited in order to demonstrate that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with DNFB. It was concluded that CpG oligonucleotides were responsible for worsening of the allergic contact dermatitis (ACD) induced by DNFB. As mentioned above with respect to Wohleben et al the issue of whether a drug is safe and has no side effects is not appropriately the

only test for enablement. Additionally, the teachings of the Satoh et al reference are not sufficient to establish a lack of enablement for the claimed invention. The ACD is caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

The Examiner has cited Dziadzio et al (Handbook of Experimental Pharmacology 2004, 161:273-285) as teaching that DNA vaccination for allergic disease requires further evaluation. However, Dziadzio et al actually teaches that CpG containing oligonucleotides are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al teach:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The teachings of Dziadzio et al as a whole do not support a finding that the claimed invention was unpredictable at the time of filing of the patent application.

A review article by Barnes (European J. Internal Medicine, 2000, 11:9-20) was also cited by the Examiner. Applicants were also directed to see Hussain et al J. Invest. Dermatol. Symp. Proc. 2004, 9:23-28 and Serebrisky et al J. Immunology, 2000, 165:5906-5912 without further comment. Barnes was cited for the teaching that "immunostimulatory oligonucleotides are potent inducers of Th1 cytokines and in mice, administration of CpG-ODN increases the ratio of Th1 to Th2 cells, decreases formation of specific IgE and reduces the eosinophilic response of allergen".... and..."that the animal studies encourage the possibility that vaccination might prevent or cure atopic disease in the future." These statements from Barnes do not support the unpredictability of

the invention. If anything these statements are consistent with and supportive of the utility of the invention.

The Examiner has cited Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred. However, it is believed that most unmethylated CpG containing oligonucleotide within the scope of the claims would have the ability to initiate *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have not been observed. For example, the Examiner has pointed to the statement on page 907 that "There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS. In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this statement the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

Applicants also pointed to a number of post-filing studies that further confirm the working examples in the pending application. Those studies reiterate, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. The Examiner stated that these studies were only post filing evidence. Applicants submit that the post-filing evidence was presented simply to rebut the Examiner's post-filing evidence of lack of enablement. Applicants do not rely on any of the post-filing references to provide enablement.

The Examiner also states that not every CpG oligonucleotide will be effective, and asks whether the *in vivo* data from one CpG molecule, SEQ ID NO: 10, indicate that all other CpG molecules will function to treat asthma. The data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) 1984, however, the court stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims. Regardless, the specification includes data on far more oligonucleotides than one. As described above, numerous oligonucleotides were tested for immune stimulatory activity.

The specification teaches that, both *in vitro* and *in vivo*, CpG containing oligonucleotides drive the immune system toward a Th1 response, and thus constitute an effective asthma treatment. This is sufficient to enable the claimed methods. Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to

produce a Th1 favored immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention.

Applicants have presented a significant amount of data in the specification and asserted on the record that such data correlates with the scope of the claimed invention. The data is summarized above. The combination of the changes in immune parameters observed and described in the specification was adequate to demonstrate to one of skill in the art at the time of the filing of the priority patent application that CpG oligonucleotides would be useful in the treatment of asthma. Applicants assert that a correlation between CpG and their use in the treatment of asthma is disclosed and enabled.

MPEP section 2164.02 teaches that

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicants have presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any objective evidence to demonstrate why it does not correlate

Claim 38 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Examiner has questioned how inflammation could be prevented, as

claimed in claim 38, if the other claims are directed to the treatment of asthma. As taught in the specification asthma is associated with inflammation and narrowing of the airways. Administration of a CpG oligonucleotide results in treatment of asthma. One of the effects of CpG oligonucleotides is to alter cytokine profiles, which may lead to the prevention of further inflammation. It is this embodiment that is claimed in claim 38.

Claims 19-39 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. According to the Office Action the specification does not adequately describe the genus of molecules encompassed by immunostimulatory oligonucleotides comprising a 5'-cytosine-guanine-3'. It was concluded that "the claims do not set forth the specific structure of the claimed immunostimulatory oligonucleotides and it is not clear if the claims or specification give the structure and a function of the immunostimulatory oligonucleotides." (Office Action pages 22-23).

The Examiner alleges that the claims do not set forth a function or specific structure for the claimed oligonucleotides. Contrary to Examiner's assertions, the claimed invention is not described solely in terms of methods of its making coupled with its function. There is a correlation between the structure of the claimed invention and its function. As discussed in the specification, the immune stimulatory effects of DNA are a result of the presence of unmethylated CpG dinucleotides in particular base contexts (CpG motifs). These immune stimulatory effects of CpG oligonucleotides (ODN) are highly CpG specific in that the effects are dramatically reduced if the CpG motif is methylated, changed to a GpC, or otherwise eliminated or altered. The claims are directed to a use of an oligonucleotide having a core CpG motif. The structures of such ODNs and their function in stimulating various types of immunogenic responses, including the treatment of asthma are described in the specification and the examples and drawings.

The ODNs of the invention are not described merely by functional characteristics. The ODNs of the invention are described by structure, formula, name, and physical properties – as ODNs with specific sequences, specific lengths, and specific internucleotide linkages. In addition, modifications to the bases, nucleosides, and the linkages as envisaged by the instant invention are

also described. Examples of specific sequences, linkages and structures of the oligonucleotides of the instant invention are shown the summary of the invention and the detailed description.

Additionally claims 23-25 recite specific hexamers or octamers and claims 26-27 recite specific formulas with defined variables. No basis has been provided for rejecting these claims which include additional structural features.

Applicants respectfully request that the Examiner withdraws the rejection under first paragraph, 35 U.S.C. §112.

Rejections Withdrawn

Applicants thank the Examiner for the acknowledgement that the rejections of claims 19-39 as being indefinite as being obvious under 35 USC 103 have been withdrawn.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: April 5, 2007

Respectfully submitted,

By _____

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